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Serotonin/FoxO Signaling in Bone Formation

Over the last few years, LRP5 has been identified as a major and potent regulator of bone mass in humans. The fundamental importance of *Lrp5* and the pathway(s) it controls in the regulation of bone formation is illustrated by the fact that loss-of or gain-of function mutations can cause two profoundly different human bone diseases. Indeed, loss-of-function mutations in *Lrp5* lead to the osteoporosis pseudoglioma syndrome, a rare, but often fatal disease characterized by low bone mass. On the other hand, gain-of-function mutations in *Lrp5* cause a high bone mass phenotype. Studies in mouse models reproducing the low bone mass human disease have indicated that LRP5 positively regulates osteoblast proliferation and bone formation through its expression in duodenal cells. Lrp5 in the duodenum inhibits serotonin synthesis by these cells. Serotonin is a powerful inhibitor of osteoblast proliferation. Landmark studies performed in model organisms have established that the transcription factor FoxO1 is the crucial mediator of serotonin in a wide spectrum of physiological processes. The basis of this proposal is our finding that serotonin suppresses osteoblast proliferation by mechanisms that require stimulation of the transcriptional activity of FoxO1. These effects of serotonin involve association of FoxO1 with other serotonin-regulated transcription factors; as well as activation of Ca2+/calmodulin-dependent protein kinase (CaMK) signaling. In this proposal we are using genetic tools to determine whether FoxO1 mediates the anti-proliferative effects of serotonin in osteoblasts in the adult and aging skeleton. Additionally, we are identifying the cellular site of serotonin-FoxO1 interaction and action in the regulation of bone mass. We are also elucidating interactions of FoxO1 with other transcription factors in conferring serotonin signaling in osteoblasts. Finally, we are investigating the role of CamK signaling as a serotonin-dependent regulator of FoxO1 actions in osteoblasts.